U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA /Serial Number:	21-661/N000
Drug Name:	RSR13 (efaproxiral) Injection (75 or 100 mg/kg)
Applicant:	Allos Therapeutics Inc.
Indication(s):	Brain metastases
Date(s):	Submission Date: December 4, 2003
	PDUFA Date: June 4, 2004
	ODAC Meeting Date: May 3, 2004
	Review Completion Date:
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I (HFD-710)
Statistical Reviewer:	Rajeshwari Sridhara, Ph.D.
Concurring Reviewer:	Kooros Mahjoob, Ph.D., Acting Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Kevin Ridenhour, M.D. & Ramzi Dagher, M.D.
Project Manager:	Ms. Christy Cottrell
Keywords:	Active control/superiority, log-rank test, post-hoc analysis, subgroup analyses, multiple endpoints, multiple comparisons, Cox regression

Table of Contents

1 Executive Summary

1.1 Conclusions and Recommendations

In this reviewer's opinion the registration study failed to demonstrate improved survival of RSR13 + whole brain radiation therapy (WBRT) over WBRT alone for patients with brain metastases. It is not evident that the apparent survival advantage observed in a single small subgroup of patients with primary breast cancer based on post-hoc analysis is attributable solely to the treatment effect and not due to imbalances in known and unknown prognostic factors. Therefore, the evidence submitted in this application based on results from a single trial, is not convincing and does not support the sponsor's claim of efficacy in a subgroup of patients with breast cancer primary.

1.2 Brief Overview of Clinical Studies

The sponsor has submitted results from one phase III, comparative clinical trial (registration trial Study RT009) comparing WBRT alone to RSR13 + WBRT, to demonstrate efficacy of RSR13. The sponsor has also provided supportive efficacy data from a phase II, single arm study (Study RT008). The main focus of this review is on results from Study RT009.

Study RT009 was a multicenter international study conducted in patients with brain metastases. This study was initiated on February 16, 2000 and the study was completed on September 24, 2002. The data cut-off date for final efficacy analysis was January 31, 2003.

Study RT009 was a phase III randomized, open-label, comparative study conducted in 538 patients from 82 international centers, who would be receiving a standard 2-week (10-day) course of WBRT for brain metastases. Patients were randomized (1:1) to receive RSR13 no longer than 30 minutes prior to daily WBRT or WBRT alone. Patients were stratified at randomization to 4 strata: (1) Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) Class I (including non-small cell lung, breast, and other primary cancers), (2) RPA Class II non-small cell lung cancer (NSCLC) primary, (3) RPA Class II breast cancer primary, and (4) RPA Class II primary tumors of various origins (hereafter referred as other primary).

1.3 Statistical Issues and Findings

This NDA submission is to support administration of RSR13 as an adjunct to whole brain radiation therapy (WBRT) for patients with brain metastases from primary breast cancer. In this NDA submission, study RT009 is the only

randomized pivotal study conducted for the efficacy and safety of RSR13. This open-label study was designed to evaluate the efficacy and safety of combined therapy with RSR13 + WBRT versus WBRT alone in patients with brain metastases. This study enrolled a total of 538 patients with 267 patients who received WBRT alone and 271 patients who received RSR13 + WBRT. The primary efficacy endpoint of this study was survival.

Statistical Issues:

1. Only one randomized open-label study conducted in patients with brain metastases, which failed to demonstrate efficacy as per the design of the study, in the intent-to-treat population (log-rank test, P-value = 0.1688) and in the co-primary subgroup of patients with NSCLC/Breast cancer primary (log-rank test, P-value = 0.1217).
2. When the overall result fails to show efficacy, usually subgroup findings are not acceptable and subgroup analyses at best can be exploratory or hypothesis generating analyses (ICH E-3 guidelines, section 11.4.2.8: *These analyses are not intended to "salvage" an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labelling information, patient selection, dose selection etc.*). When one starts to do multiple subgroups testing, one can easily make a false positive claim based on such subgroup analysis. We do not know how to interpret the P-values based on such post-hoc analysis. Furthermore, without replication of the results in a second well-controlled study, the subgroup analysis can not be ruled out for a false positive result.
3. The sponsor wishes to claim approval based on a subgroup of patients with primary breast cancer. This subgroup hypothesis corresponding to breast cancer primary patients was not stated as a hypothesis of interest to be tested in the original protocol. Any subgroup hypothesis needs to be stated in the protocol and accordingly proper allocation of α has to be specified. Otherwise, such post-hoc subgroup claim will inflate Type I error and it is difficult to interpret such P-values.
4. Some of the important issues not addressed by the sponsor are: imbalance in patients who were ineligible (per protocol) between the two treatment groups; misclassification of patients in the randomized strata; imbalance in the number of baseline brain lesions in the subgroup of patients with primary breast cancer.

Findings:

The protocol specified primary analysis was unadjusted log-rank test in the intent-to-treat (ITT) population to compare overall survival between the two treatment

arms. This study failed to demonstrate survival benefit as presented in the following Table A.

Table A: Primary Efficacy Survival Analysis in ITT Population

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	221/267	**4.5** (3.7, 5.4)	0.877 (0.727, 1.057)	**0.1688**
RSR13 + WBRT	220/271	**5.3** (4.5, 6.2)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT; [3]: unadjusted log-rank test.

The sponsor amended the protocol during the course of study to include a co-primary hypothesis, to test survival difference between the two treatment arms in a subgroup of patients with NSCLC or Breast primary cancer. The results of these comparisons also failed to demonstrate survival benefit as presented in Table B below.

Table B: Co-Primary Efficacy Survival Analysis in NSCLC/Breast Primary Cancer Subgroup*

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	167/206	**4.5** (3.8, 5.4)	0.844 (0.680, 1.048)	**0.1217**
RSR13 + WBRT	164/208	**5.9** (4.7, 7.0)		

*: Corrected for miss-classification (i.e., non-randomized subgroup); [1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT; [3]: unadjusted log-rank test.

The sponsor is seeking approval based on post-hoc analysis in a small subgroup of 115 patients with Breast cancer primary. The results of these comparisons are presented in the following Table C.

Table C: Exploratory Survival Analysis in the Subgroup of Patients with Primary Breast Cancer*

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	47/55	**4.6** (3.8, 6.2)	0.552 (0.359, 0.850)	**0.0061**
RSR13 + WBRT	39/60	**8.7** (6.0, 11.3)		

*: Corrected for miss-classification (i.e., non-randomized subgroup);
[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test and not adjusted for multiple analyses.

2 Introduction

2.1 Overview

It has been estimated that in the United States 80,000 to 170,000 patients develop brain metastases each year. Standard palliative treatment for symptomatic lesions consists of corticosteroids and whole brain radiation therapy (WBRT). Analysis of a large database compiled by the Radiation Therapy Oncology Group (RTOG) indicates that the overall prognosis of patients with brain metastasis is poor with median survival time of 4-7 months.

2.1.1 Background

RSR13 is a synthetic allosteric modifier of hemoglobin. RSR13 emulates the function of natural allosteric modifiers such as 2,3-diphosphoglycerate (2,3-DPG). RSR13 is a small molecule that reduces hemoglobin-oxygen binding affinity, described by an increase in p50 (the partial pressure of oxygen [pO_2] that results in 50% hemoglobin saturation), and enhances the diffusion of oxygen from the blood to the tissues.

Radiation therapy is currently the principal non-surgical therapy to achieve local control of brain metastases from solid tumors. However, the efficacy of radiation therapy (RT) is modified by the extent of tumor oxygenation. Hypoxic tumors are more resistant to cell damage by radiation and tumor hypoxia adversely affects the clinical prognosis of RT. It has been reported in literature that tumors with a low median pO_2 have a higher in-field failure rate after RT.

Animal pharmacology studies have shown that RSR13 increases blood p50, increases pO_2 in non-tumor and tumor tissue, and increases oxygen diffusive transport in non-tumor tissue. The effect of RSR13 on hemoglobin in the red blood cell to enhance oxygen unloading from hemoglobin, and the diffusion of that oxygen from the vascular compartment into the hypoxic tumor cells is the basis for the radioenhancement effect of RSR13. RSR13 does not need to diffuse into the brain tissue, because oxygen readily diffuses across the blood brain barrier and the cancer cell membrane to increase tumor oxygenation, thereby increasing the effectiveness of RT. The goal of adjunctive RSR13 therapy in cancer patients is to increase tumor O_2 concentration thereby maximizing the cytotoxicity of the treatment modality (RT and/or chemotherapy).

The sponsor has submitted results from one phase III, randomized, controlled, open-label clinical trial (registration trial Study RT009) comparing WBRT alone to RSR13 + WBRT, to demonstrate efficacy of RSR13. The sponsor has also

provided supportive efficacy data from a phase II, single arm study (Study RT008). The main focus of this review will be on results from Study RT009.

2.1.2 Major Statistical Issues

1. Only one randomized open-label study conducted in patients with brain metastases, which failed to demonstrate efficacy as per the design of the study, in the intent-to-treat population (log-rank test, P-value = 0.1688) and in the co-primary subgroup of patients with NSCLC/Breast cancer primary (log-rank test, P-value = 0.1217).
2. When the overall result fails to show efficacy, usually subgroup findings are not acceptable and subgroup analyses at best can be exploratory or hypothesis generating analyses (ICH E-3 guidelines, section 11.4.2.8: *These analyses are not intended to "salvage" an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labelling information, patient selection, dose selection etc.*). When one starts to do multiple subgroups testing, one can easily make a false positive claim based on such subgroup analysis. We do not know how to interpret the P-values based on such post-hoc analysis. Furthermore, without replication of the results in a second well-controlled study, the subgroup analysis can not be ruled out for a false positive result.
3. The sponsor wishes to claim approval based on a subgroup of patients with primary breast cancer. This subgroup hypothesis corresponding to breast cancer primary patients was not stated as a hypothesis of interest to be tested in the original protocol. Any subgroup hypothesis needs to be stated in the protocol and accordingly proper allocation of α has to be specified. Otherwise, such post-hoc subgroup claim will inflate Type I error and it is difficult to interpret such P-values.
4. Some of the important issues not addressed by the sponsor are: imbalance in patients who were ineligible (per protocol) between the two treatment groups; misclassification of patients in the randomized strata; imbalance in the number of baseline brain lesions.

2.2 Data Sources

Data used for review is from the electronic submission received on 12/3/03. The network path is \\Cdsesub1\n21661\N_000\2003-12-03\crt\datasets. Specifically, datasets from Study 009 were reviewed (\\Cdsesub1\n21661\N_000\2003-12-03\crt\datasets\rt009).

3 Statistical Evaluation

3.1 Evaluation of Efficacy

The sponsor has submitted efficacy results from the following two studies:

a) Study RT008: A phase II non-randomized, open-label single arm study conducted in 69 patients from 17 centers (16 US, 1 Canada), to evaluate the safety and efficacy of RSR13 with WBRT in patients with brain metastases.
b) Study RT009: A phase III randomized, open-label, comparative study conducted in 538 patients from 82 centers (40 US, 15 Canada, 4 Australia, 4 Hungary, 3 Belgium, 3 France, 3 Germany, 3 Israel, 2 Italy, 2 Scotland, 2 Spain and 1 UK), to evaluate safety and efficacy of RSR13 with WBRT compared to WBRT alone in patients with brain metastases.

Reviewer's Comment:

Study RT008 is a non-randomized, single arm, open-label study and as such can not evaluate efficacy based on overall survival. Therefore, this review will focus only on the randomized Study RT009 and particularly on the efficacy aspect of this study. Please refer to the clinical review of this application for the evaluation of Study RT008.

3.1.1 Study RT009

Study RT009 was a multicenter international study conducted in patients with brain metastases. This study was initiated on February 16, 2000 and the study was completed on September 24, 2002. The data cut-off date for final efficacy analysis was January 31, 2003.

3.1.1.1 Study Design

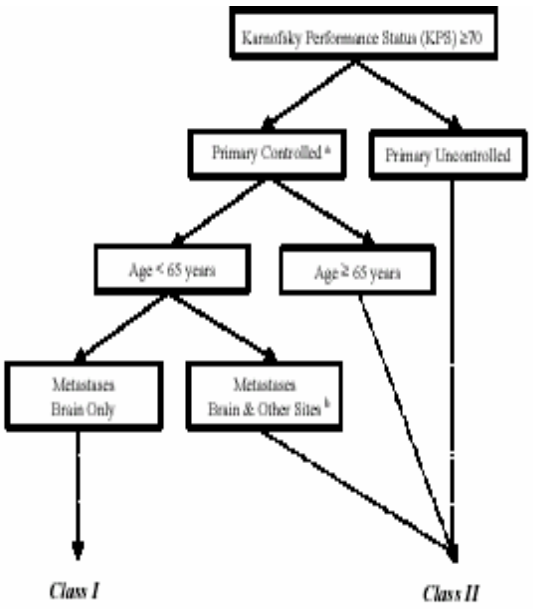
Study RT009 was a phase III, randomized, open-label, comparative study in patients who would be receiving a standard 2-week (10-day) course of WBRT for brain metastases. Patients were randomized (1:1) to receive RSR13 no longer than 30 minutes prior to daily WBRT or WBRT alone. Patients were stratified at randomization to 4 strata: (1) Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) Class I (including non-small cell lung, breast, and other primary cancers), (2) RPA Class II non-small cell lung cancer (NSCLC) primary, (3) RPA Class II breast cancer primary, and (4) RPA Class II

primary tumors of various origins (hereafter referred as other primary). The decision tree utilized in the RPA classification is illustrated in Figure 1.

Eligibility criteria included that all patients should have Karnofsky Performance Status (KPS) = 70, radiographic studies consistent with brain metastases and a histologically or cytologically confirmed primary malignancy. Patients with small cell lung cancer, extrapulmonary small cell carcinomas, germ cell tumors or lymphomas were excluded from entering the study. Patients included in the study were not to have received prior treatment for brain metastases with WBRT, sterotactic radiosurgery, chemotherapy, hormonal therapy, immunotherapy, or biological agents.

All patients were to be assessed for safety from randomization until the initial follow-up visit at 1 month after completion of the radiation therapy (RT) course. Standard follow-up visits were required 3 months after the completion of RT course and every 3 months thereafter until progression, and then followed for subsequent therapies and survival.

Figure 1: RPA Classification Decision Tree



[a] Primary controlled : those cases for which there was radiographic documentation of no tumor growth over a minimum of 1 month, thus requiring 2 separate examinations, the second of which was performed within 2 months prior to randomization.

Reviewer's Comments:

1. It was clearly stated in the protocol that the randomized stratification was purely for balance between treatment groups and therefore the number of patients in each of the four strata would not be predetermined.
2. There were a total of 23 ineligible patients (17 patients in the WBRT alone arm and 6 patients in the RSR13 + WBRT arm) based on eligibility criteria at entry, who were entered into the study and treated (Please refer to Appendix 1 for the list of ineligible patients by treatment arm). There were greater than 2 times more patients who were ineligible in the control arm compared to the RSR13 arm. Given the open-label nature of the study there is concern for bias due to the apparent imbalance in ineligible patients between the two arms.
3. There were a total of 25 patients who were miss-classified in the strata assignment at randomization (please refer to Appendix 2 for a complete list of miss-classified patients). This miss-classification is not an issue when analyzing the overall intent-to-treat (ITT) population (all patients as randomized to the two treatment groups) using unadjusted analysis. However, this miss-classification can lead to biased results when considering adjusted analysis because the true patient strata will no longer be as randomized. In particular, there were 6 patients where there were major miss-classifications: 2 patients who were randomized as RPA II, breast cancer were later re-classified as RPA II, NSCLC; 1 patient who was randomized as NSCLC was later re-classified as RPA II, other; and 3 patients who were randomized as RPA II, other were later re-classified as RPA II, NSCLC.

3.1.1.2 Treatment Administration

Daily administration of RSR13 required placement of a central venous access device (CVAD). RSR13 treatment arm patients received supplemental oxygen (4L/min via nasal cannula) beginning 5 minutes prior to initiation of infusion, during infusion and WBRT, and for at least 15 minutes after completion of daily WBRT. Patients in the control arm of the study did not receive a placebo. Starting dose and dosing adjustment thereafter of RSR13 was based on gender, weight and oxygen saturation measured by standard pulse oximetry (SpO_2). Starting dose of RSR13 in this study was 75 or 100 mg/kg. The dosing instructions were amended 2 times during the course of the study. Patients with SpO_2 while breathing room air on any WBRT day < 90% were not treated with RSR13. Before the second amendment, if SpO2 while breathing room air at screening (at rest and during exercise) and on WBRT day 1 was = 93% then RSR13 100mg/kg was administered. If SpO2 while breathing room air at screening (at rest and during exercise) and on WBRT day 1 was 90-92% then

RSR13 75mg/kg was administered. After the second protocol amendment, if SpO2 while breathing room air at screening (at rest and during exercise) and on WBRT day 1 was = 93% then RSR13 was administered based on gender and weight as follows: (a) Males (i) if weight = 95kg then 100 mg/kg; (ii) if weight > 95kg then 75 mg/kg, and (b) Females (i) if weight = 70kg then 100 mg/kg; (ii) if weight > 70kg then 75 mg/kg.

Reviewer's comment:

The dosing regimen was changed during the course of study based on weight and gender. Therefore it will be difficult to determine the optimum dose that is efficacious based on the results of this study.

3.1.1.3 Study Objectives

The study objectives were: (1) to determine the effect of RSR13 on primary and secondary efficacy endpoints in patients with brain metastases receiving daily IV doses of RSR13 administered immediately prior to standard whole brain radiation therapy compared to patients receiving standard whole brain radiation therapy alone, and (2) to determine the safety of RSR13 in this patient population.

3.1.1.4 Efficacy Endpoints

Primary Efficacy Endpoint of this study was survival. Secondary Efficacy Endpoints included time to radiographic and time to clinical tumor progression in the brain, response rate in the brain, cause of death, and quality of life.

Reviewer's Comment:

In the original protocol (Jan 10, 2000), efficacy was to be established based on the primary endpoint of survival in the intent-to-treat total population. Subsequently in amendment 2 (June 5, 2001) *per sponsor* after enrollment of a total of *222* patients (*172* patients in the NSCLC/breast primary subgroup), the protocol was amended to include a co-primary analysis in the subgroup of patients with NSCLC and breast primary cancer. This reviewer's analysis suggested that by June 5, 2001 there were a total of *173* patients (*134* patients in NSCLC/Breast primary subgroup) enrolled into the study (Appendix 4). The only reasoning given by the sponsor to include this subgroup as a co-primary was that the group

of patients with NSCLC/breast primary tumors comprised a large and homogenous subpopulation of patients. Given the open-label nature of this study such additions of primary hypotheses are of concern.

3.1.1.5 Sample Size Considerations

In the original protocol (Jan 10, 2000), a sample size requirement of a total of **408** eligible patients was estimated based on the following assumptions: a mix of 20% RPA class I and 80% RPA class II patients, median survival in WBRT to be 4.57 months, an expected 35% increase in median survival in WBRT with RSR13 (median survival of 6.17 months), 18 months of accrual, a shape parameter of 0.20, and 80% power to detect the difference in survival at two-sided overall significance level of 0.05. It was estimated that a total of **308 deaths** from both arms would be required to detect the survival difference in the overall ITT population. It was expected that there might be 5% ineligible patients and therefore a total of 408 patients were required to be entered on the study.

This sample size calculation was amended in amendment 2 (June 5, 2001) as follows: The sample size was increased to a total of **501** patients in order to observe **402 deaths** by increasing the power of the study to detect the survival difference (median survival 4.57 months versus 6.17 months in the overall ITT population) to 85%, increasing accrual time to 27 months, and changing the shape parameter to zero (O'Brien and Fleming). In this amendment the sponsor also **added a co-primary analysis in the subgroup of patients with NSCLC/breast primary tumors.** It was stated that in this subgroup a total of **308** deaths will be required to provide a power of 75% with a two-sided significance level of 0.05. Furthermore, in this amendment it was stated that the expected number of patients to be enrolled into the study would be between 501-538 patients, depending on the percentage of patients with 'other' as a primary cancer. If 25% of enrolled patients had 'other' primary, then a total of 501 patients would be enrolled; if 30% of enrolled patients had 'other' primary, then a total of 538 patients would be enrolled.

Reviewer's Comments:

1. Reason for changing the space parameter was not specified in the amendment.
2. There was no specific scientific reason given to include a co-primary in the subgroup of patients with NSCLC/breast primary other than that this was a large, homogenous subgroup.
3. A total of 538 patients were enrolled in this study. Only 23% of the patients had 'other' primary tumors.

3.1.1.6 Interim Analysis

In the original protocol (Jan 10, 2000) it was stated that, one interim analysis of the primary study endpoint (overall survival), would be conducted. The interim analysis was planned to be performed when 50% of expected events *(154 deaths)* occurred.

In the first amendment of the protocol (Mar 2, 2000) the section on interim analysis was revised to state that a stochastic analysis would be performed at the time of interim analysis and reported to Data Safety Monitoring Committee (DSMC). It was also stated in this amendment that if the significance level of the log-rank test between treatment arms was less than *0.0077* then the null hypothesis would be rejected. Additionally, if the stochastic analysis indicated less than 15% power to observe the alternative hypothesis, then enrollment to the study may be recommended to be stopped.

In the second amendment of the protocol (June 5, 2001), this section was again revised. It stated that interim status and safely reports will be prepared for the independent DSMC every 6 months until planned study enrollment was achieved. Furthermore, with the revised increase in sample size, the interim analysis for efficacy was to be conducted when 50% events (*201 deaths*) had occurred in the total patient population. The results of interim analysis would be reported to the DSMC. If the significance level of the log-rank test between treatment arms was less than *0.0052* then the null hypothesis would be rejected and the DSMC might recommend stopping enrollment to the study. On the other hand if the analysis indicated less than 15% power to observe the alternative hypothesis, then also it may be recommended to stop further accrual.

Reviewer's Comment:

It appears that one interim efficacy analysis was conducted (March 22, 2002). Specific results of this interim analysis or DSMC meeting minutes deliberating on interim efficacy results have not been submitted (Refer to Appendix 5 for FDA analysis). Because of this interim analysis, the significance level for testing at the time of final analysis needs to be adjusted to maintain an overall family-wise level of significance of 0.05.

3.1.1.7 Efficacy Analysis Methods

Primary Efficacy Analysis:

In the original protocol (dated Jan 10, 2000), it was specified that the primary endpoint, overall survival, measured from the time of randomization into the study, would be *compared between treatment arms by unadjusted log-rank test*. The median survival time would be estimated in both treatment arms. Other specific point estimates of clinical interest for each treatment were 6-month and 1-year survival. It was stated that additional subgroup analyses would be performed if there were sufficient numbers of patients across subgroups. RPA class, site of primary cancer, and other important covariates such as primary tumor control, age, presence of extracranial metastases, baseline KPS, and number of metastatic lesions, would be included in a multivariate Cox model along with treatment arm to test the relative importance of these factors for survival.

In the first amendment of the protocol (dated March 2, 2000), it was specified that the primary final analysis of the study would be undertaken when all patients have been potentially followed for a minimum of 6 months and the planned number of deaths (308) had been observed. The primary analysis would be conducted on an *intent-to-treat* patient population using log-rank statistic *(unadjusted for covariates*) and *evaluable subgroup analyses might be performed to provide supportive evidence of efficacy*.

In the second (dated June 5, 2001, sample size increased, co-primary added) and third (dated October 9, 2001) amendments of the protocol, it was specified that the primary final analysis would be undertaken when the planned number of deaths in both the total study population (402) and the NSCLC/breast subpopulation (308) had been observed. The primary analysis would be conducted *on an intent-to-treat basis* and *evaluable subgroup analyses might be performed to provide supportive evidence of efficacy*. Furthermore, it was stated that a modified Bonferroni adjustment for multiple comparisons (co-primary analyses) would be made. The *adjusted significance level* for the final analysis after accounting for one interim analysis was set *at 0.048.*

The statistical analysis plan (SAP) which was finalized on July 29, 2002, revised the analysis data set and specified that the analysis data set will consist of *eligible patients only*. The SAP specified that: (1) patients without brain metastases, patients with leptomenigeal metastases, patients with confirmed primaries of small cell lung cancer, extrapulmonary small cell carcinomas, germ cell tumors and lymphomas and (2) patients having prior treatment for brain metastases with WBRT or stereotactic radiosurgery, and patients with prior surgical resection of brain metastases with no remaining lesions would be ineligible and would be excluded from analysis. The SAP also stated that the primary analysis of the

overall patient population as well as the NSCLC/breast subpopulation would be performed *using the unadjusted log-rank test*.

In the SAP the list of covariates that would be included in the Cox-model was also revised. It stated that the following covariates would be included: age (continuous as well as above and below 65 years old), baseline weight (divided by gender as per the dosing guidelines of amendment 2), number of cranial metastases (1, 2-3, 4 or more), baseline cranial tumor total area, gender, RPA class, site of primary cancer, primary tumor control, number of extracranial metastases (0, 1-2, 3 or more), presence of liver metastases, usage of subsequent treatment (systemic vs. non-systemic, any vs. none), baseline KPS, diagnosis timing (definition to follow), prior treatment for cranial metastases (yes/no; prior treatment may delay time from diagnosis to radiation therapy), worldwide location (USA vs. Canada vs. others, North America vs. Others), altitude, baseline hemoglobin, and size of center. Center size was the binary variable designating a center as large or small. Under the section on covariates, the SAP also stated that '*While designated prospectively, supporting analyses should be considered exploratory in nature, and inferences made based on p-values should be done so with caution. Primary reasons for exploratory analyses are for estimation rather than hypothesis testing*'.

Secondary Efficacy Analyses:

The protocol has specified that the secondary endpoints, time to radiographic tumor progression in brain and time to clinical tumor progression in the brain, would be analyzed using cumulative incidence model and that the treatment arms would be compared using the method of Pepe. It is also stated that analyses within strata, within other prognostic groups and Cox model analysis would also be performed.

Secondary endpoint response rate (best maximal response) in the brain would be determined from MRI or CT scans and the frequency distribution of CR:PR:SD:PD would be compared for each treatment arm. Between treatment arms comparison would be made using Cochran-Mantel Haenzel test.

Regarding secondary endpoint cause of death, frequency of neurologic/ non-neurologic/ undistinguishable deaths would be computed for each treatment arm and compared between treatment arms using Cochran-Mantel Haenzel test.

Secondary endpoint of quality of life would be determined by the Spitzer Questionnaire and KPS assessment. The frequency distribution would be computed for each treatment arm by time of follow-up.

Reviewer's Comments:

1. In the original protocol and in its amendments it was clearly stated that the primary analysis would be conducted in ITT population. The sample size and the power considerations were in fact based on ITT population.
2. The co-primary hypothesis testing in the NSCLC/Breast subgroup was added during the course of study. The protocol did not clearly define this subgroup, i.e., whether patients from strata 2 and 3 only to be included in this subgroup or include NSCLC/Breast primary patients in strata 1, and strata 2 and 3.
3. In using Modified Bonferroni adjustment for co-primary analysis one could consider 2 methods of adjustment after accounting for one interim analysis: (1) compare larger of the 2 p-values with 0.048, (a) if the larger p-value is < 0.048, then reject both hypotheses, or (b) if the larger p-value is > 0.048, then compare the smaller of the two p-values with 0.024 (Hochberg's SU modified Bonferroni procedure), or (2) the second procedure (Holm's SD modified Bonferroni) is (a) if the smaller of the two p-values is > 0.024, then both hypotheses are not significant, or (b) if the smaller of the p-value < 0.024 then the corresponding hypothesis is significant and then test if the larger of the p-value is < 0.048.
4. In the original protocol and in its amendments as well as in the SAP, it was clearly stated that the primary analysis would be based on unadjusted log-rank test.
5. The SAP was finalized after all the patients were entered into the study (last 3 patients were entered on July 29, 2002). Given the open-label nature of the study it is of concern that the analysis population was changed after all patients were entered into the study.
6. Overall there were 23 patients who were ineligible, 17 in the control arm and 6 in the RSR13 arm. With greater than 2 times more patients who were ineligible in the control arm, given the study was an open-label study, there is concern for bias.
7. There was no justification provided for the inclusion of additional several covariates for the exploratory Cox analysis in the SAP.
8. The covariate 'diagnosis timing' was not defined.
9. Because no apriori probability of type I error allocation has been specified, analyses of secondary efficacy endpoints can only be considered as exploratory and supportive to primary efficacy analysis.

3.1.1.8 Sponsor's Results and Statistical Reviewer's Findings/ Comments

In the RT009 study, a total of 538 patients were randomized to receive WBRT alone (267 patients) or RSR13 followed by WBRT (271 patients).

3.1.1.8.1 Baseline Characteristics

Table 1 lists the number of patients entered in each of the randomized strata. The baseline Characteristics of the overall population and NSCLC/Breast subgroup are presented in Tables 3 & 4.

Reviewer's Comments:

1. There were 25 patients who were miss-classified at randomization according to the sponsor / CRF. Therefore the corrected numbers in each of the strata are presented in Table 2.
2. It should be noted that the patients as listed in each strata in Table 2 are no longer as randomized.
3. This miss-classification may not affect analysis based on ITT population. However analyses based on subgroups could potentially lead to biased results.
4. The sponsor has reported that 9 patients (4 in the control (WBRT) arm and 5 in the RSR13 arm) withdrew from the study prior to WBRT day 1 (Appendix 3).
5. In the overall patient population the baseline characteristics appear to be balanced between the two treatment arms.
6. It should be noted that *the NSCLC/Breast subgroup* as presented in Table 3 *is no longer as randomized*, because: (1) NSCLC and breast cancer patients from the Strata 1, RPA class I, are included in this subgroup, and (2) patients who were miss-classified in the incorrect stratum at randomization are re-classified into corrected primary tumors based on the reported diagnosis in CRF.

Table 1: Number of Patients as Randomized in Each Stratum by Treatment Arm

Strata	WBRT	RSR13 + WBRT	Total
RPA Class I	28 (10.5%)	29 (10.7%)	57 (10.6%)
RPA Class II, NSCLC	132 (49.4%)	132 (48.7%)	264 (49.1%)
RPA Class II, Breast	51 (19.1%)	52 (19.2%)	103 (19.1%)
RPA Class II, Other	56 (21.0%)	58 (21.4%)	114 (21.2%)

Table 2: Number of Patients as Observed in Each Stratum by Treatment Arm

Strata	WBRT	RSR13 + WBRT	Total
RPA Class I	24 (9.0%)	22 (8.1%)	46 (8.6%)
RPA Class II, NSCLC	136 (50.9%)	133 (49.1%)	269 (50.0%)
RPA Class II, Breast	50 (18.7%)	56 (20.7%)	106 (19.7%)
RPA Class II, Other	57 (21.3%)	60 (22.1%)	117 (21.7%)

Table 3: Baseline Characteristics in ITT Population

Characteristic	WBRT	WBRT + RSR13
Gender: Female	150 (56.2%)	153 (56.5%)
Male	117 (43.8%)	118 (43.5%)
Race: Caucasian	239 (89.5%)	242 (89.3%)
Non-Caucasian	28 (10.5%)	29 (10.7%)
Age Group: < 65 years	197 (73.8%)	196 (72.3%)
= 65 years	70 (26.2%)	75 (27.7%)
Age in yrs: Mean (S.D.)	57.0 (11.0)	57.1 (11.1)
Median (Range)	57 (23 – 81)	57 (30 -87)
Weight in Kg: Mean (S.D.)	72.5 (17.1)	71.3 (15.0)
Median (Range)	70.5 (33 – 140.9)	71.0 (39.8 – 122)
KPS Group: < 90	124 (46.4%)	113 (41.7%)
= 90	143 (53.6%)	158 (58.3%)
KPS: Mean (S.D.)	85.2 (9.7)	85.1 (9.7)
Bidirectional product (mm^2) for baseline lesions: Mean (S.D.)	760.8 (694.8)	753.6 (735)
Median (Range)	587.5 (4, 4200)	518 (16, 5080)
Resting SpO_2: Mean (S.D.)	96.8 (1.7)	96.7 (1.8)
Primary Controlled : No	200 (74.9%)	199 (73.4%)
Yes	67 (25.1%)	72 (26.6%)
Extracranial metastases: 0	96 (36.0%)	84 (31.0%)
1	69 (25.8%)	72 (26.6%)
2	55 (20.6%)	56 (20.7%)
= 3	47 (17.6%)	59 (21.7%)
Number of Brain Lesions: 1	53 (20.2%)	45 (16.9%)
2	81 (30.9%)	82 (30.7%)
= 3	128 (48.9%)	140 (52.4%)
Liver Metastases: No	225 (84.3%)	217 (80.1%)
Yes	42 (15.7%)	54 (19.9%)
Lung Metastases: No	183 (68.5%)	179 (66.1%)
Yes	84 (31.5%)	92 (33.9%)
Synchronous Disease: No	184 (68.9%)	183 (67.5%)
Yes	83 (31.1%)	88 (32.5%)
Prior Brain Mets Treatment: No	238 (89.1%)	250 (92.3%)
Yes	29 (10.9%)	21 (7.7%)
Hemoglobin (g/dL): Mean (S.D.)	13.5 (1.5)	13.3 (1.5)
Creatinine (mg/dL): Mean (S.D.)	0.79 (0.23)	0.76 (0.21)
Albumin (g/dL): Mean (S.D.)	3.70 (0.45)	3.65 (0.47
ALT (IU/L): Mean (S.D.)	40.9 (34.2)	40.5 (49.4)
Primary Site: NSCLC	151 (56.5%)	148 (54.6%)
Breast	55 (20.6%)	60 (22.1%)
Other	61 (22.9%)	63 (23.3%)

Table 4: Baseline Characteristics in NSCLC/Breast* Subgroup

Characteristic	WBRT	WBRT + RSR13
Gender: Female	130 (63.1%)	128 (61.5%)
Male	76 (36.9%)	80 (38.5%)
Race: Caucasian	184 (89.3%)	184 (88.5%)
Non-Caucasian	22 (10.7%)	24 (11.5%)
Age Group: < 65 years	150 (72.8%)	150 (72.1%)
= 65 years	56 (27.2%)	58 (27.9%)
Age in yrs: Mean (S.D.)	57.1 (11.2)	56.9 (11.0)
Median (Range)	57 (26 – 81)	57 (31 – 80)
Weight in Kg: Mean (S.D.)	70.7 (15.9)	71.1 (15.0)
Median (Range)	68.8 (33 – 124.1)	69.6 (41.1 – 122)
KPS Group: < 90	89 (43.2%)	87 (41.8%)
= 90	117 (56.8%)	121 (58.2%)
KPS: Mean (S.D.)	85.7 (9.5)	85.1 (9.6)
Bidirectional product (mm^2) for baseline lesions: Mean (S.D.)	755.6 (668.2)	767.8 (767.8)
Median (Range)	573.5 (17 – 3806)	459 (16 – 5080)
Resting SpO_2: Mean (S.D.)	96.9 (1.7)	96.8 (1.8)
Primary Controlled : No	156 (75.7%)	159 (76.4%)
Yes	50 (24.3%)	49 (23.6%)
Extracranial metastases: 0	76 (36.9%)	75 (36.0%)
1	51 (24.8%)	54 (26.0%))
2	42 (20.4%)	42 (20.2%)
= 3	37 (18.0%)	37 (17.8%)
Number of Brain Lesions: 1	43 (21.1%)	37 (18.0%)
2	60 (29.4%)	66 (32.2%)
= 3	101 (49.5%)	102 (49.8%)
Liver Metastases: No	176 (85.4%)	176 (84.6%)
Yes	30 (14.6%)	32 (15.4%)
Lung Metastases: No	148 (71.8%)	155 (74.5%)
Yes	58 (28.2%)	53 (25.5%)
Synchronous Disease: No	140 (68.0%)	133 (63.9%)
Yes	66 (32.0%)	75 (36.1%)
Prior Brain Mets Treatment: No	189 (91.8%)	197 (94.7%)
Yes	17 (8.2%)	11 (5.3%)
Hemoglobin (g/dL): Mean (S.D.)	13.4 (1.5)	13.4 (1.4)
Creatinine (mg/dL): Mean (S.D.)	0.77 (0.22)	0.75 (0.20)
Albumin (g/dL): Mean (S.D.)	3.7 (0.4)	3.6 (0.5)
ALT (IU/L): Mean (S.D.)	39.2 (33.0)	41.9 (54.4)

*: Revised group per reclassification (corrected) and including RPA Class I patients.

3.1.1.8.2 Primary Efficacy Analyses

Primary efficacy analysis per original protocol, comparing overall survival between WBRT and RSR13 + WBRT, in the ITT population using unadjusted log-rank test is presented in Table 5 (same as reported by the sponsor). There were a total of 441/538 patients who had events (deaths) at the time of the final analysis. The Kaplan-Meier curves for the ITT population are illustrated in Figure 2. The efficacy analysis in the subgroup of NSCLC/Breast primary patients is presented in Table 6 (same as reported by the sponsor). The Kaplan-Meier curves for the NSCLC/Breast subgroup is presented in Figure 3. There were 331/414 deaths in this subgroup at the time of the final analysis.

Table 5: Primary Efficacy Survival Analysis in ITT Population

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	221/267	**4.5** (3.7, 5.4)	0.877 (0.727, 1.057)	**0.1688**
RSR13 + WBRT	220/271	**5.3** (4.5, 6.2)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test.

Figure 2: Kaplan-Meier Survival Curves in the ITT Population

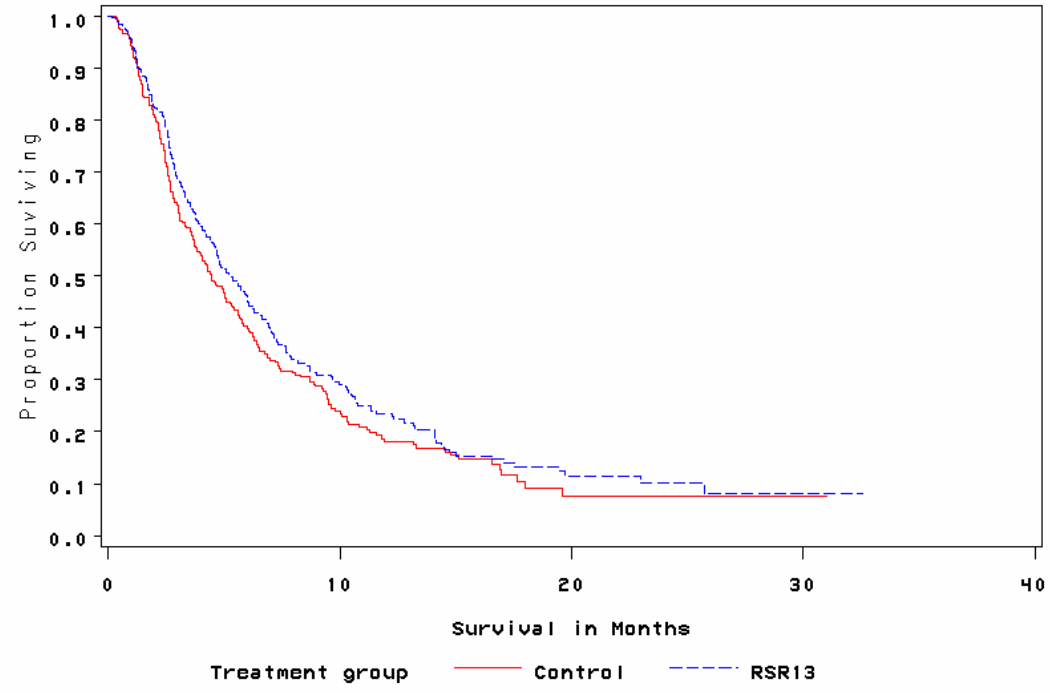
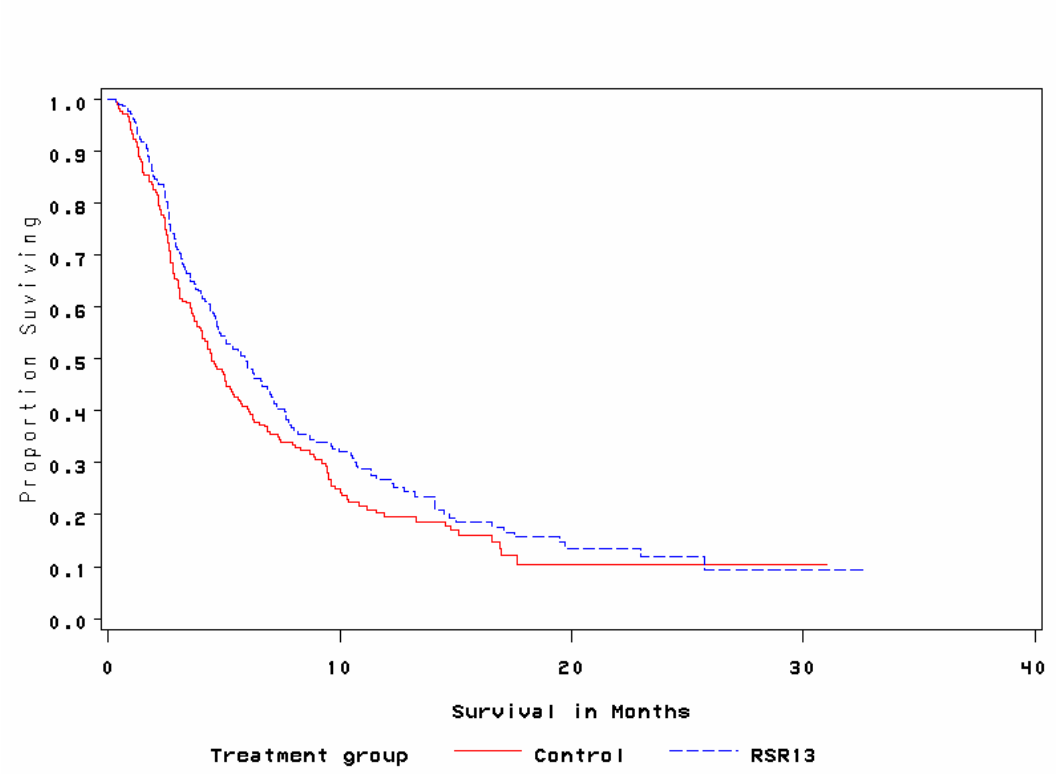


Table 6: Co-Primary Efficacy Survival Analysis in NSCLC/Breast Primary Cancer Subgroup*

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	167/206	**4.5** (3.8, 5.4)	0.844 (0.680, 1.048)	**0.1217**
RSR13 + WBRT	164/208	**5.9** (4.7, 7.0)		

*: Corrected for miss-classification (i.e., non-randomized subgroup);
[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test.

Figure 3: Kaplan-Meier Survival Curves in the Subgroup of Patients with NSCLC/Breast Primary



Reviewer's Comments:

1. **RSR13 + WBRT treatment failed to demonstrate superior survival over WBRT alone in the randomized ITT population** (Table 5 and Figure 2 above). The final analysis was conducted after observing the required number of deaths (required 402 deaths, observed 441 deaths)

specified in the protocol. The median survival in the WBRT arm was slightly less than what was expected in the protocol design.

2. **RSR13 + WBRT treatment failed to demonstrate superior survival over WBRT alone in the subgroup of patients with NSCLC/Breast primary** (*Co-primary analysis*, Table 6 and Figure 3 above). The final analysis was conducted after observing the required number of deaths (required 308 deaths, observed 331 deaths) specified in the protocol.
3. There appears to be an imbalance between the treatment arms in the number of patients who were not eligible (17 in the WBRT alone arm and 6 in the RSR13 + WBRT arm). The results of exploratory analyses in eligible patients only or per-protocol patients in the overall population and in the NSCLC/Breast primary subgroup of patients are presented respectively, in the following Tables 7 and 8. These results also fail to demonstrate superior survival of RSR13 + WBRT treatment over WBRT alone.
4. There were 30/441 early deaths within 1 month from the start of the study. Of the 30 deaths 16 were in the WBRT alone arm (2 Breast, 11 NSCLC and 3 Other primaries), and 14 were in the RSR13 + WBRT arm (4 Breast, 3 NSCLC and 7 Other primaries). It appears that there were more early deaths in the control arm compared to RSR13 arm in the NSCLC and breast primary subgroups. Given these numerical differences and open-label nature of the study it is uncertain if bias was introduced in patient selection and allocation.

Table 7: Exploratory Survival Analysis in the Per-Protocol Overall Population

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	206/250	**4.4** (3.7, 5.3)	0.871 (0.719, 1.054)	**0.1549**
RSR13 + WBRT	215/265	**5.4** (4.6, 6.3)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test and not adjusted for multiple analyses.

Table 8: Exploratory Survival Analysis in the Per-Protocol NSCLC/Breast Primary Cancer Subgroup*

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	157/194	**4.4** (3.7, 5.2)	0.815 (0.654, 1.017)	**0.0693**
RSR13 + WBRT	159/203	**6.0** (4.7, 7.1)		

*: Corrected for miss-classification (i.e., non-randomized subgroup);
[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test and not adjusted for multiple analyses.

3.1.1.8.3 Exploratory Covariate Adjusted and Subgroup Survival Analyses

The sponsor had specified exploratory covariate adjusted survival analyses using Cox model. The sponsor had also specified exploratory survival analyses in each of the randomized strata. In this section the results of these exploratory analyses are presented.

In the original protocol and its amendments, 7 covariates were mentioned as likely to be included in the Cox model (Refer to section 3.1.1.7, and Table 9 below). After completion of accrual this analysis was revised in the SAP to include 18 covariates (Refer to section 3.1.1.7, and Table 9 below) in various combinations of continuous and categorical variables resulting in 48 Cox models (submitted by sponsor including 17/18 covariates, all models included the same 17 covariates, not presented here). Results of Cox regression analysis including the 7 covariates specified in the protocol are presented in Table 11 (FDA analysis). One of the models including the 18 covariates in the per-protocol population as specified in the SAP is presented in Table 12 (FDA analysis).

Table 9: Covariates Intended to be Included in the Cox Model

Protocol Covariates	**SAP Covariates**
RPA Class	RPA Class
Site of Primary Cancer	Site of Primary Cancer
Primary Tumor Control	Primary Tumor Control
Age	Age
Presence of Extracranial Metastases	
Baseline KPS	Baseline KPS
Number of Metastatic Lesions	Number of Cranial Metastases
	Number of Extracranial Metastases
	Baseline Cranial Tumor Total Area
	Baseline Weight (divided by gender as per the dosing guidelines)
	Gender
	Presence of Liver Metastases
	Usage of Subsequent Treatment*
	Diagnosis Timing
	Prior Treatment to Cranial Metastases
	Worldwide Location
	Altitude
	Baseline Hemoglobin
	Size of Center

* Not included in sponsor's adjusted Cox models

Table 10: Cox's Proportional Hazard Model Adjusting for Covariates in the ITT Population (Protocol Planned Model)

Covariates	Hazard Ratio	95% C.I.	P-value[1]
Treatment (RSR13 + WBRT/WBRT)	0.814	0.674, 0.984	0.0335
RPA Class (1 vs. 2)	0.742	0.471, 1.168	0.1973
Site of Primary Cancer: Breast (Yes vs. No)	0.568	0.423, 0.764	0.0002
NSCLC (Yes vs. No)	0.861	0.682, 1.085	0.2050
Primary Tumor Control (Yes vs. No)	1.310	1.006, 1.707	0.0453
Age	1.014	1.005, 1.023	0.0022
Presence of Extracranial Metastases (No vs. Yes)	1.138	0.800, 1.618	0.4732
Baseline KPS	0.968	0.958 – 0.978	< 0.0001
Number of Metastatic Lesions[2]	1.287	1.111 – 1.490	0.0008

1: P-values not adjusted for multiplicity; 2: Since all patients were supposed to have brain metastases, for the purpose of this analysis 'number of extracranial metastases' was used as the covariate in place of 'number of metastatic lesions'.

Table 11: Cox's Proportional Hazard Model Adjusting for Covariates in the Overall Eligible Patient Population (SAP Planned Model)*

Covariates	Hazard Ratio	95% C.I.	P-value[1]
Treatment (RSR13 + WBRT/WBRT)	0.777	0.640, 0.942	0.0103
RPA Class (1 vs. 2)	0.763	0.479, 1.215	0.2547
Site of Primary Cancer: Breast (Yes vs. No)	0.602	0.430, 0.842	0.0031
NSCLC (Yes vs. No)	0.826	0.640, 1.065	0.1409
Primary Tumor Control (Yes vs. No)	1.238	0.927, 1.652	0.1481
Age Group (< 65 vs. = 65 yrs)	1.486	1.178, 1.875	0.0008
Baseline KPS Group (= 90 vs. < 90)	1.564	1.283, 1.907	< 0.0001
Number of Cranial Metastases	1.148	1.000, 1.320	0.0508
Number of Extracranial Metastases	1.237	1.102, 1.389	0.0003
Baseline Cranial Tumor Total Area (<250, 250-1000, > 1000)	1.071	0.930, 1.233	0.3418
Baseline Weight Group (Low vs. High)	0.971	0.765, 1.232	0.8096
Gender (Female vs. Male)	1.407	1.120, 1.767	0.0033
Presence of Liver Metastases (No vs. Yes)	1.249	0.941, 1.658	0.1232
Usage of Subsequent Treatment (No vs. Yes)	0.910	0.695, 1.192	0.4937
Diagnosis Timing (metachronous vs. synchronous)	1.122	0.870, 1.448	0.3737
Prior Treatment to Cranial Metastases (No vs. Yes)	0.450	0.302, 0.671	< 0.0001
Worldwide Location: USA (No vs. Yes)	0.921	0.665, 1.275	0.6199
Canada (No vs. Yes)	0.919	0.639, 1.322	0.6505
Altitude (Low vs. High)	1.096	0.805, 1.491	0.5604
Baseline Hemoglobin Group (= 12 vs. < 12 g/dL)	1.336	1.027, 1.738	0.0308
Size of Center (Not a big site vs. Big site)	0.965	0.762, 1.222	0.7679

*: Results based on a total of 528 patients; [1]: P-values not adjusted for multiplicity;

Reviewer's Comments:

1. Some of the covariates included in the model are likely to be highly correlated. For example, RPA Classification takes into account whether primary was controlled or not, age and whether there was metastasis in brain only or not.
2. The models specified by the sponsor both in the protocol and in SAP are ambiguous and questionable. In the protocol specified model, the meaning of the covariate, number of metastatic lesions, is unclear. One could interpret it as total number of metastases (cranial + extracranial metastases), or number of brain lesions. Furthermore both the number of cranial lesions, extracranial metastases, and baseline tumor area appear like continuous variables, but in fact are categorized as zero, 1, 2 or 3. Regarding baseline cranial tumor area, the variable included in the model was the variable submitted by the sponsor as 'GBDPTOT' and the explanation given for this variable is that it is bi-dimensional product for baseline lesions. It is assumed in the above analysis that these are measurements for cranial lesions only. The covariate, diagnosis timing, was not defined in the protocol. The sponsor had used this as a categorical variable: synchronous diagnosis or not. One could interpret it as the actual time in days to the diagnosis of brain metastasis.
3. Scientific basis or literature citation in choosing these covariates (either in the protocol or SAP) for the model was not provided by the sponsor. Some of the important covariates, such as, response to steroid treatment, systemic tumor activity, LDH, interval between primary tumor and development of brain metastases, reported in literature as significant prognostic factors for survival, were not included in these analyses and data needed for such evaluation were not collected.
4. Furthermore, when appropriately adjusted for multiplicity, treatment differences are unlikely to be significant. P-values from these exploratory covariate analyses can not be taken at face value.
5. Results from Cox regression analyses including only the randomized strata are presented in Tables 12-14. The treatment effect was not significant in any of these models. Please refer to Appendix 6 for exploratory Cox regression analyses in NSCLC/Breast Primary subgroup.
6. The sponsor did not include the covariate 'usage of subsequent therapy' (as specified in the final SAP) in their Cox models

Table 12: Cox's Proportional Hazard Model Adjusting for Strata (As Randomized) in the ITT Population

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (RT + RSR vs. RT)	0.871	0.722 – 1.050	0.1484
Stratum 2** = RPA Class 2, Primary Lung	1.638	1.175 – 2.284	0.0036
Stratum 3** = RPA Class 2, Primary Breast	1.388	0.954 – 2.022	0.0870
Stratum 4** = RPA Class 2, Primary Other	2.142	1.488 – 3.083	< 0.0001

* P-values not adjusted for multiplicity; ** Strata as randomized (25 patients were miss-classified)

Table 13: Cox's Proportional Hazard Model Adjusting for Re-classified Strata in the ITT Population

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (RT + RSR vs. RT)	0.879	0.729 – 1.061	0.1799
Stratum 2** = RPA Class 2, Primary Lung	1.436	1.003 – 2.056	0.0479
Stratum 3** = RPA Class 2, Primary Breast	1.158	0.777 – 1.726	0.4714
Stratum 4** = RPA Class 2, Primary Other	1.933	1.313 – 2.846	0.0008

* P-values not adjusted for multiplicity; ** Strata as observed or intended (25 patients were re-classified)

Table 14: Cox's Proportional Hazard Model Adjusting for Primary Site (Including RPA Class I and Primary Site as Observed) in the ITT Population

Covariates	Hazard Ratio	95% C.I.	P-value*
Treatment (RT + RSR vs. RT)	0.893	0.740, 1.077	0.2362
Primary Lung	0.774	0.617, 0.969	0.0258
Primary Breast	0.618	0.466, 0.821	0.0009

* P-values not adjusted for multiplicity

7. Exploratory survival analyses results in each of the primary site subgroups (NSCLC, Breast, and Other) are presented in Tables 15-17 (results same as reported by the sponsor) and Kaplan-Meier Curves are illustrated in Figures 4-6.

Table 15: Exploratory Survival Analysis in the Subgroup of Patients with Primary NSCLC

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	120/151	**4.4** (3.5, 5.7)	0.991 (0.771, 1.273)	**0.9426**
RSR13 + WBRT	125/148	**4.9** (4.1, 6.2)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test and not adjusted for multiple analyses.

Figure 4: Kaplan-Meier Curves in the Subgroup of Patients with Primary NSCLC

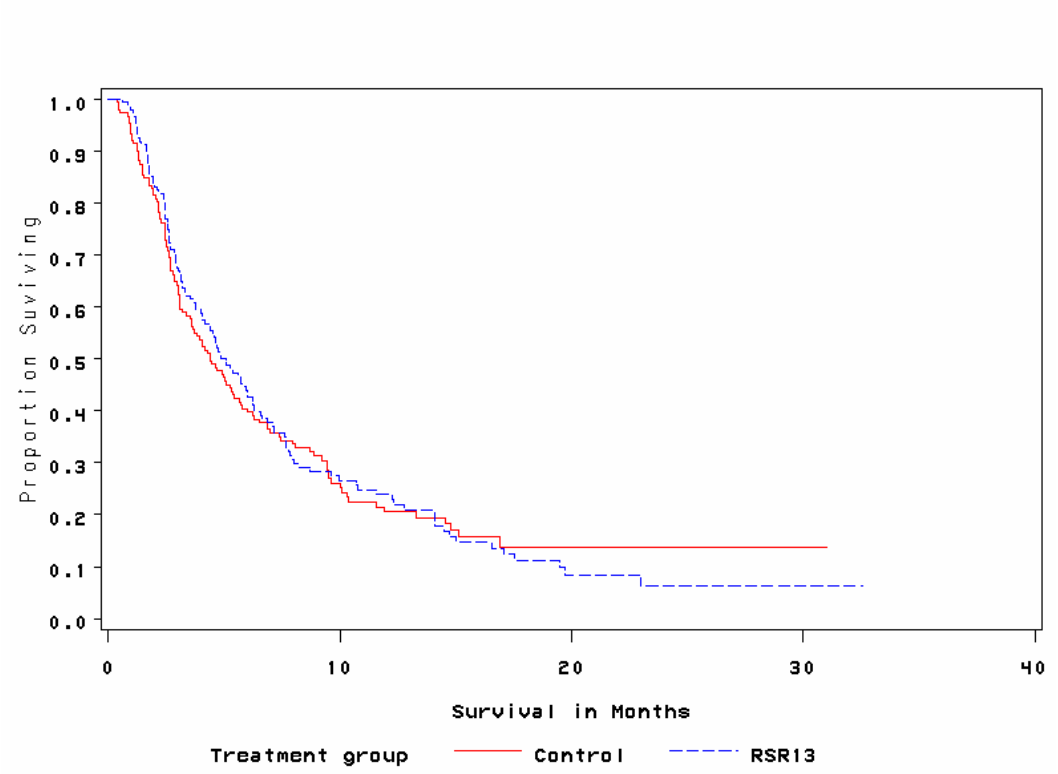


Table 16: Exploratory Survival Analysis in the Subgroup of Patients with Primary Breast Cancer

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	47/55	**4.6** (3.8, 6.2)	0.552 (0.359, 0.850)	**0.0061**
RSR13 + WBRT	39/60	**8.7** (6.0, 11.3)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test and not adjusted for multiple analyses.

Figure 5: Kaplan-Meier Curves in the Subgroup of Patients with Primary Breast Cancer

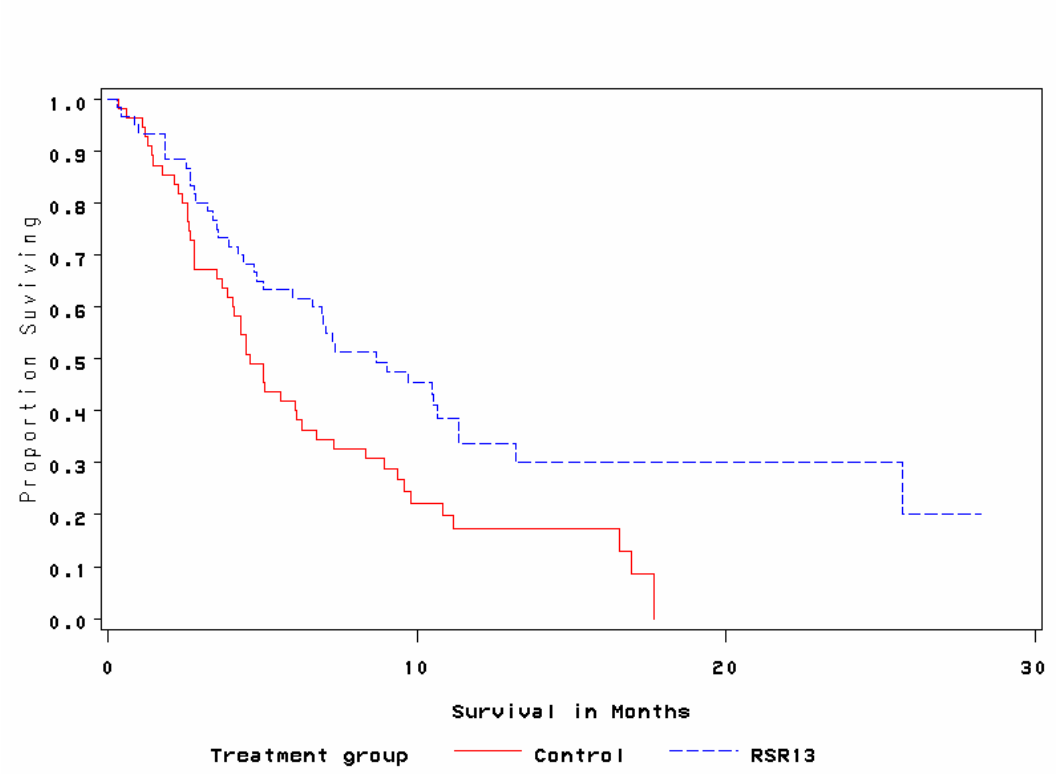
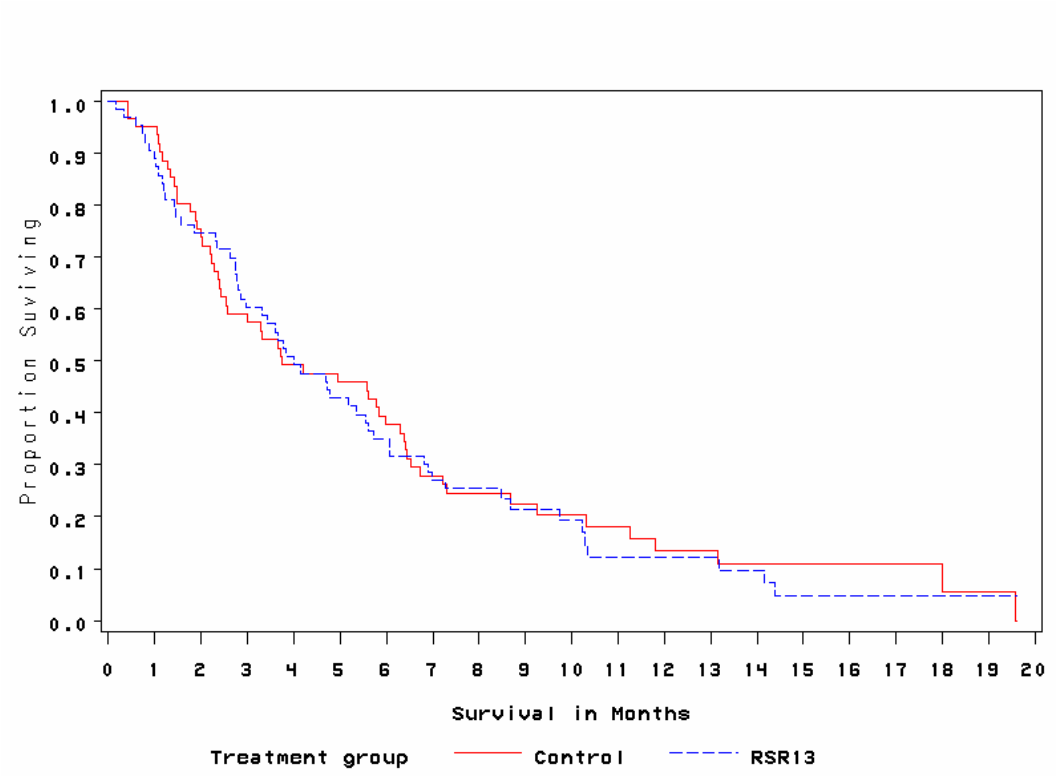


Table 17: Exploratory Survival Analysis in the Subgroup of Patients with Primary 'Other' Cancer

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	54/61	**3.7** (2.5, 6.0)	1.029 (0.708, 1.496)	**0.8812**
RSR13 + WBRT	56/63	**4.0** (2.9, 5.6)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test and not adjusted for multiple analyses.

Figure 5: Kaplan-Meier Curves in the Subgroup of Patients with Primary 'Other' Cancer



8. Any subgroup analysis results are relevant only if overall study (ITT) is positive.
9. Hypotheses testing in these subgroups, and a allocation for testing these subgroup hypotheses were not prespecified. Therefore, the P-values obtained in these subgroup analyses are not interpretable without a prespecified significance level.

10. There were no significant differences in the treatment effect in the subgroups of patients with primary NSCLC or Other Cancer.
11. The apparent treatment difference observed in the subgroup of patients with primary breast cancer can only be considered as hypothesis generating. The efficacy claim in this non-randomized, non-prespecified subgroup is based on post-hoc, data driven hypothesis testing in a very small subgroup (115 patients in total) of patients from a single study.
12. Well-controlled studies are required to approve a drug (21 CFR 314.126(a): *Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs*). Large, well conducted, controlled, randomized study is required particularly when considering single study for consideration of approval.
13. The Guidance for Industry: Providing clinical evidence of effectiveness from human drug and biological products (May 1998) clearly states that: '*When considering whether to rely on a single multicenter trial, it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single multicenter trial*'.
14. Furthermore, of the 115 patients with breast primary, 8 patients (6 in WBRT arm and 2 in the RSR13 +WBRT arm) were not eligible patients (did not meet the inclusion criteria), 7 patients (3 in WBRT arm and 4 in RSR13 + WBRT arm) were misclassified, 1 patient in the control arm was withdrawn from the study prior to receiving any treatment, 6 patients (2 in WBRT arm, 4 in RSR13+WBRT arm) were dead within one month, and 15 patients (8 in WBRT arm, 7 in RSR13 + WBRT arm) were dead within 2 months from the start of the study. Among the patients who were terminated early in the RSR13 arm, 1 patient received only one dose, 5 patients received 2 doses only, and 2 patients received 5 doses only.
15. There appears to be imbalance in some of the baseline patient characteristics favoring the RSR13 + WBRT arm compared to WBRT alone arm in the subgroup of patients with breast primary. These baseline characteristics include, weight, performance status = 90, tumor burden, 3 or more extracranial metastases, 3 or more brain lesions, presence of lung metastases and prior brain metastases treatment (Table 18 below, bolded characteristics). Please refer to the clinical review of this application for other imbalances such as, differences in oxygen administration between the two treatment arms in the subgroup of patients with breast cancer primary.
16. Furthermore, in the breast primary subgroup majority were younger (< 65 years old) women with metachronous diagnosis compared to the other subgroups.
17. Without replication of the results in a second well-controlled study, the subgroup analysis can not be ruled out for a false positive result.

18. ICH E– 3, Section 11.4.2.8, clearly specifies guidelines for conducting subgroup analyses, namely, '***These analyses are not intended to "salvage" an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labelling information, patient selection, dose selection etc.'*** Therefore, (a) Examining a subgroup of patients with primary breast cancer when the overall study is not-supportive, is not acceptable; (b) Because the randomized strata have been modified, the subgroup under consideration is not a randomized subgroup; (c) Apparent imbalances between the treatment groups with respect to some of the baseline characteristics may potentially be driving the difference in survival.
19. Although no drug has been approved for breast cancer patients with brain metastasis, in general the approval of drugs in advanced breast cancer are based on relatively large studies.

Table 18: Baseline Characteristics in Breast* Subgroup

Characteristic	WBRT	WBRT + RSR13
Gender: Female	54 (98.2%)	60 (100.0%)
Male	1 (1.8%)	0 (0.0%)
Race: Caucasian	48 (87.3%)	50 (83.3%)
Non-Caucasian	7 (12.7%)	10 (16.7%)
Age Group: < 65 years	45 (81.8%)	48 (80.0%)
= 65 years	10 (18.2%)	12 (20.0%)
Age in yrs: Mean (S.D.)	53.9 (11.2)	52.0 (11.6)
Median (Range)	53 (30-78)	51 (31-80)
Weight in Kg: Mean (S.D.)	**68.2 (17.5)**	**73.2 (14.7)**
Median (Range)	**64 (42-124.1)**	**72.9 (46.5-122)**
KPS Group: < 90	24 (43.6%)	24 (40.0%)
= 90	**31 (56.4%)**	**36 (60.0%)**
KPS: Mean (S.D.)	85.3 (9.2)	85.5 (9.6)
Bidirectional product (mm^2) for baseline lesions: Mean (S.D.)	**882.1 (695.1)**	**761.9 (705.8)**
Median (Range)	**699 (17-3588)**	**578.5 (16-2936)**
Resting SpO_2: Mean (S.D.)	97.5 (1.8)	96.9 (1.7)
Primary Controlled : No	37 (67.3%)	41 (68.3%)
Yes	18 (32.7%)	19 (31.7%)
Extracranial metastases: 0	8 (14.6%)	7 (11.7%)
1	8 (14.6%)	14 (23.3%)
2	17 (30.9%)	20 (33.3%)
= 3	**22 (40.0%)**	**19 (31.7%)**
Number of Brain Lesions: 1	5 (9.3%)	13 (21.7%)
2	9 (16.7%)	13 (21.7%)
= 3	**40 (74.1%)**	**34 (56.7%)**
Liver Metastases: No	36 (65.5%)	39 (65.0%)
Yes	19 (34.5%)	21 (35.0%)
Lung Metastases: No	23 (41.8%)	31 (51.7%)
Yes	**32 (58.2%)**	**29 (48.3%)**
Synchronous Disease: No	53 (96.4%)	58 (96.7%)
Yes	2 (3.6%)	2 (3.3%)
Prior Brain Mets Treatment: No	**51 (92.7%)**	**58 (96.7%)**
Yes	4 (7.3%)	2 (3.3%)
Hemoglobin (g/dL): Mean (S.D.)	13.0 (1.6)	12.7 (1.2)
Creatinine (mg/dL): Mean (S.D.)	0.78 (0.28)	0.67 (0.12)
Albumin (g/dL): Mean (S.D.)	3.9 (0.5)	3.7 (0.42)
ALT (IU/L): Mean (S.D.)	36.4 (29.5)	40.4 (44.9)

*: Revised group per reclassification (corrected) and including RPA Class I patients.

3.1.1.8.4 Secondary Efficacy Analyses

Results submitted by the sponsor on the evaluation of secondary efficacy endpoints will be briefly summarized in this section. The protocol specified secondary endpoints were time to radiographic and time to clinical tumor progression in the brain, response rate in the brain, cause of death, and quality of life.

Time to Radiographic Tumor Progression in the Brain

Time to radiographic tumor progression, as determined by Central Radiology Review, was estimated for all patients using cumulative incidence analysis and Kaplan-Meier methods, and tested between treatment arms using Gray's test. Death in this analysis was recorded as a competing risk when it occurred prior to diagnosis of radiographic progression.

Per sponsor's report, there was no statistically significant difference in the cumulative incidence of radiographic progression between the WBRT alone and RSR13 + WBRT arms ($?^2 = 0.458$, **p-value = 0.4986**). The sponsor has also reported that there was no statistically significant difference in the cumulative incidence of radiographic progression between the WBRT alone and RSR13 + WBRT arms in the subset of patients with NSCLC primary (p-value = 0.8142), or Breast primary (p-value = 0.8023) or Other primary (p-value = 0.3597).

Time to Clinical Progression in the Brain

Time to clinical tumor progression, was estimated for all patients using cumulative incidence analysis and Kaplan-Meier methods, and tested between treatment arms using Gray's test. Death in this analysis was recorded as a competing risk when it occurred prior to diagnosis of clinical progression.

Per sponsor's report, there was no statistically significant difference in the cumulative incidence of clinical progression between the WBRT alone and RSR13 + WBRT arms ($?^2 = 0.595$, **p-value = 0.4407**). The sponsor has also reported that there was no statistically significant difference in the cumulative incidence of clinical progression between the WBRT alone and RSR13 + WBRT arms in the subset of patients with NSCLC primary (p-value = 0.8142), or Breast primary (p-value = 0.8023) or Other primary (p-value = 0.3597).

Response Rate in the Brain

Best response was determined from MRI or CT scans performed at each follow-up visit. The distribution of best response in the brain was compared between the treatment arms using Cochran-Mantel-Haenzel test.

According to the sponsor, 455 patients had a scan after the baseline scan, in whom response could be assessed. The sponsor has reported that there was no statistically significant difference in the distribution of response between the treatment arms in this group of patients (**p-value = 0.1226**).

Cause of Death

The sponsor has stated that cause of death was an inadequate endpoint for meaningful analysis. However they have reported that by the Cochran-Mantel-Haenzel test there was no difference in the distribution of cause of death between the two treatment arms (**p-value = 0.5090**). The following table was presented by the sponsor describing the cause of death.

Table 19: Cause of Death by Treatment Arms

Cause of Death	**WBRT (N = 267)**	**RSR13 + WBRT (N = 271)**
Neurologic	34	37
Non-neurologic	128	128
Indistinguishable	58	53
Missing/Withdrew Consent	1	2
Still Alive	46	51

Quality of life

Quality of life (QOL) was determined with the KPS assessment and the Spitzer Questionnaire that were performed at baseline, WBRT day 10, and all routine follow-up visits. Comparisons of QOL measures between treatment arms focused on the 6-month and 12-month time-points and did not included WBRT day 10.

The sponsor has reported that in the overall population, the distributions of KPS scores were similar at all time-points between the two treatment arms and no statistically significant differences were observed in the distribution of KPS scores between the treatment arms at 6 months or 1 year using the Cochran-Mantel-Haenzel test (**p-value =0.1540, p-value=0.1831**, respectively).

Spitzer Questionnaire scores were based on 5 questions each worth 0-2 points for a total of possible 10 points. Patients with at least 3 of the 5 questions answered were given a scaled total score equivalent to the average score per question multiplied by 5. The scores at 6-month and 1-year follow-up visits were compared to baseline for each patient and categorized as stable or increasing, decreased by 1-2 points, or decreased by more than 2 points. The distribution of

these categories at 6 months and 1 year was compared between treatment arms using Cochran-Mantel-Haenzel test.

The sponsor has reported that in the overall population, the distributions of Spitzer Questionnaire scores were similar at all time-points between the two treatment arms and no statistically significant differences were observed in the distribution of Spitzer Questionnaire scores between the treatment arms at 6 months or 1 year using the Cochran-Mantel-Haenzel test (**p-value =0.3118, p-value=0.196**1, respectively).

Reviewer's Comments:

1. **None of the secondary efficacy analyses demonstrated superior treatment effect of RSR13 + WBRT compared to WBRT alone.**
2. Discrepancies in the responses between the sponsor and FDA Clinical reviewer was observed. For details of further response evaluation and analyses, please refer to Clinical Review of this application.
3. Because significant proportion of patients had cause of death as indistinguishable, it is difficult to interpret these results.
4. In analyzing and interpreting the results of the QOL measures one should be cautious. Given that the median survival in this study is between 4.5 to 5.3 months, comparing treatment differences at 6 months or at 1 year can result in biased results with many missing measurements.

3.2 Evaluation of Safety

Please refer to Clinical Review of this application for safety evaluation.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

Efficacy by gender was analyzed by conducting an exploratory survival analysis. The results of this analysis are presented in Table 20. Efficacy by age (< 65 years vs. = 65 years was also analyzed by conducting exploratory survival analysis. The results of this analysis are presented in Table 21. Because majority (approximately 90%) of the patients entered in the study were Caucasians, efficacy by race was not evaluated.

Table 20: Exploratory Survival Analysis by Gender in the ITT Population

Gender	Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
Females	WBRT	120/150	**5.0** (4.3, 6.3)	0.821 (0.635, 1.062)	**0.1313**
	RSR13 + WBRT	116/153	**6.9** (4.8, 8.2)		
Males	WBRT	101/117	**3.7** (3.0, 5.1)	0.947 (0.720, 1.245)	**0.6943**
	RSR13 + WBRT	104/118	**4.3** (3.3, 5.6)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test and not adjusted for multiple analyses.

Table 21: Exploratory Survival Analysis by Age Group in the ITT Population

Age Group	Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
< 65 yrs	WBRT	157/197	**5.4** (4.2, 6.4)	0.905 (0.726, 1.130)	**0.3781**
	RSR13 + WBRT	158/196	**5.8** (4.8, 6.9)		
= 65 yrs	WBRT	64/70	**3.2** (2.8, 4.2)	0.802 (0.564, 1.141)	**0.2176**
	RSR13 + WBRT	62/75	**3.8** (3.0, 4.7)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test and not adjusted for multiple analyses.

Reviewer's Comments:

1. There was no significant treatment effect in either female or male patients. However, females appear to have longer survival than males.
2. There was no significant treatment effect in either less than 65 years old patients or 65 or older patients. However, younger patients (< 65 years) appear to have longer survival than older patients (= 65 years).

4.2 Other Special/Subgroup Populations

Effect by weight group adjusted for gender (RSR13 dose of 100mg/kg if male and = 95 kg or if female and = 70 kg (low weight group), otherwise RSR13 dose of 75 mg/kg (larger weight)) was evaluated by conducting an exploratory survival analysis. The results of this analysis are presented in Table 22.

Exploratory survival analysis in patients with brain disease only (primary disease controlled and no extracranial metastases, N = 67), did not demonstrate RSR13 effect (Hazard Ratio = 0.959, 95% C.I.: 0.538, 1.707, p-value = 0.8859). For the evaluation of efficacy in other specific subgroup population please refer to section 3.1.1.8.3.

Table 22: Exploratory Survival Analysis by Weight Group in the ITT Population

Weight Group	**Treatment**	**Number of Deaths**	**Median Survival in Months[1] (95% C.I.)**	**Hazard Ratio[2] (95% C.I.)**	**P-value[3]**
= 95 kg if Male or = 70 kg if Female	WBRT	163/198	**4.4** (3.6, 5.2)	0.933 (0.752, 1.156)	**0.5240**
	RSR13 + WBRT	170/204	**4.7** (3.9, 5.9)		
> 95 kg if Male or > 70 kg if Female	WBRT	57/67	**5.0** (3.1, 8.3)	0.715 (0.488, 1.049)	**0.0841**
	RSR13 + WBRT	50/67	**6.8** (5.0, 10.5)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test and not adjusted for multiple analyses.

Reviewer's Comments:

There was no significant treatment effect in high or low weight group of patients. However, higher weight group appears to have longer survival than lower weight group of patients.

5 Summary and Conclusions

This NDA submission is to support administration of RSR13 as an adjunct to whole brain radiation therapy (WBRT) for patients with brain metastases from primary breast cancer. In this NDA submission, study RT009 is the only randomized pivotal study conducted for the efficacy and safety of RSR13. This open-label study was designed to evaluate the efficacy and safety of combined therapy with RSR13 + WBRT versus WBRT alone in patients with brain metastases. This study enrolled a total of 538 patients with 267 patients who received WBRT alone and 271 patients who received RSR13 + WBRT. The primary efficacy endpoint of this study was survival. There was no statistically significant difference between the two treatment arms in the ITT population (log-rank test, P-value=0.1688). There was apparent difference in survival between the two treatment arms in the non-randomized subgroup of patients with primary breast cancer (log-rank test, P-value=0.006).

5.1 Statistical Issues and Collective Evidence

1. Only one randomized open-label study conducted in patients with brain metastases, which failed to demonstrate efficacy as per the design of the study, in the intent-to-treat population (log-rank test, P-value = 0.1688). The final analysis was conducted after observing the planned number of total deaths.

2. The study also failed to demonstrate efficacy in the subgroup of patients with NSCLC/Breast primary (log-rank test, P-value=0.1217), which was added as a co-primary analysis subgroup during the course of study.

3. When the overall result fails to show efficacy, usually subgroup findings are not acceptable and subgroup analyses at best can be exploratory or hypothesis generating analyses (ICH E-3 guidelines, section 11.4.2.8: *These analyses are not intended to "salvage" an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labelling information, patient selection, dose selection etc.*). When one starts to do multiple subgroup testing, one can easily make a false positive claim based on such subgroup analysis. We do not know how to interpret the P-values based on such post-hoc analysis. Furthermore, without replication of the results in a second well-controlled study, the subgroup analysis can not be ruled out for a false positive result.

4. The sponsor wishes to claim approval based on a subgroup of non-randomized patients with primary breast cancer. This subgroup hypothesis corresponding to breast cancer primary was not stated as a hypothesis of interest to be tested

in the original protocol. Any subgroup hypothesis needs to be stated in the protocol and accordingly proper allocation of α has to be specified. Otherwise, such post-hoc subgroup claim will inflate Type I error and it is difficult to interpret such P-values.

5. There appears to be imbalances between the treatment arms favoring the RSR13 arm in the subgroup of patients with primary breast cancer. Specifically imbalances were observed in the number of brain lesions, tumor burden, amount of oxygen received and subsequent therapy (please refer to clinical review). The imbalances may potentially be driving the difference in survival in the subgroup.

6. Sponsor's analyses adjusted for covariates are questionable. Results of such adjusted analyses are sensitive to inclusion or exclusion of a covariate. Furthermore, when appropriately adjusted for multiplicity, treatment differences are unlikely to be significant. P-values can not be taken at face value and non-prespecified subgroup analyses are not interpretable.

7. The claims of improved efficacy in the primary breast cancer subgroup could be a false positive result and requires future studies to evaluate this hypothesis. In fact, the sponsor is currently conducting a study of WBRT versus RSR13 + WBRT in patients with brain metastases from breast cancer.

5.2 Conclusions and Recommendations

In this reviewer's opinion the study failed to demonstrate benefits of RSR13 + WBRT over WBRT alone for patients with brain metastases. According to the usual requirement of the Agency for approval for marketing a new drug, the sponsor needs to demonstrate the efficacy of the new drug in at least two independent well-controlled clinical trials. In case that there is only one pivotal efficacy study, like this NDA submission, the evidence of the drug efficacy needs to be much stronger to be convincing. Furthermore, it is not evident that the observed apparent survival advantage in a single small subgroup of patients with primary breast cancer based on post-hoc analysis is attributable solely to the treatment effect and not due to imbalances in known and unknown prognostic factors. Therefore, the evidence submitted in this application is not convincing and does not support the sponsor’s claim of efficacy.

APPENDICES

Appendix 1: List of Ineligible Patients

Patient ID	Treatment Arm	Primary Cancer
RT-009-008-1025	WBRT	Breast
RT-009-013-3065	WBRT	Breast
RT-009-013-3092	WBRT	Breast
RT-009-036-3068	WBRT	Breast
RT-009-042-1020	WBRT	Breast
RT-009-042-3015	WBRT	Breast
RT-009-018-2069	WBRT	NSCLC
RT-009-036-2163	WBRT	NSCLC
RT-009-042-2048	WBRT	NSCLC
RT-009-133-2227	WBRT	NSCLC
RT-009-142-2190	WBRT	NSCLC
RT-009-144-1043	WBRT	NSCLC
RT-009-010-4055	WBRT	Other
RT-009-018-4012	WBRT	Other
RT-009-077-4040	WBRT	Other
RT-009-127-4088	WBRT	Other
RT-009-136-4108	WBRT	Other
RT-009-023-3016	RSR13 + WBRT	Breast
RT-009-136-3072	RSR13 + WBRT	Breast
RT-009-009-2025	RSR13 + WBRT	NSCLC
RT-009-077-2263	RSR13 + WBRT	NSCLC
RT-009-130-2101	RSR13 + WBRT	NSCLC
RT-009-138-4103	RSR13 + WBRT	Other

Appendix 2: List of Patients Who Were Misclassified at Randomization

Patient ID	Treatment Arm	RPA Class	Stratum[1] as Enrolled/ Randomized	Stratum[1] as Observed/ Intended	Primary Cancer per CRF
RT-009-003-3020	WBRT	1	3	1	Breast
RT-009-003-3020	WBRT	2	1	3	Breast
RT-009-003-3020	WBRT	2	**3**	**2**	NSCLC
RT-009-003-3020	WBRT	2	**4**	**2**	NSCLC
RT-009-003-3020	WBRT	2	**4**	**2**	NSCLC
RT-009-003-3020	WBRT	2	1	2	NSCLC
RT-009-003-3020	WBRT	2	1	4	Other
RT-009-003-3020	WBRT	2	1	4	Other
RT-009-003-3020	WBRT	2	1	3	Breast
RT-009-003-3020	WBRT	2	**3**	**2**	NSCLC
RT-009-003-3020	WBRT	1	2	1	NSCLC
RT-009-003-3020	WBRT	2	1	2	NSCLC
RT-009-003-3020	WBRT	2	**2**	**4**	Other
RT-009-003-3020	RSR13 + WBRT	2	1	4	Other
RT-009-003-3020	RSR13 + WBRT	2	1	3	Breast
RT-009-003-3020	RSR13 + WBRT	2	1	3	Breast
RT-009-003-3020	RSR13 + WBRT	1	2	1	NSCLC
RT-009-003-3020	RSR13 + WBRT	1	2	1	NSCLC
RT-009-003-3020	RSR13 + WBRT	2	1	4	Other
RT-009-003-3020	RSR13 + WBRT	2	1	4	Other
RT-009-003-3020	RSR13 + WBRT	2	1	3	Breast
RT-009-003-3020	RSR13 + WBRT	2	1	2	NSCLC
RT-009-003-3020	RSR13 + WBRT	2	**4**	**2**	NSCLC
RT-009-003-3020	RSR13 + WBRT	2	1	3	Breast
RT-009-003-3020	RSR13 + WBRT	2	1	2	NSCLC

[1]: Stratum Classification: 1 = RPA Class I; 2 = RPA Class II, NSCLC primary; 3 = RPA Class II, Breast primary; 4 = RPA Class II, Other primary.

Appendix 3: List of Patients Who Were In-evaluable (Withdrew from Study Prior to Treatment)

Patient ID	Treatment Arm	Primary Cancer (CRF)
RT-009-008-1025	WBRT	Breast
RT-009-023-2127	WBRT	NSCLC
RT-009-004-4015	WBRT	Other
RT-009-018-4012	WBRT	Other
RT-009-019-2105	RSR13 + WBRT	NSCLC
RT-009-035-2131	RSR13 + WBRT	NSCLC
RT-009-036-2232	RSR13 + WBRT	NSCLC
RT-009-041-2249	RSR13 + WBRT	NSCLC
RT-009-007-4069	RSR13 + WBRT	Other

Appendix 4: Survival Analysis Before Addition of Co-primary Hypothesis

Survival Analysis in Patients Enrolled Before Addition of Co-primary

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	43/86	**4.3** (2.8, 7.2)	0.903 (0.587, 1.389)	**0.6408**
RSR13 + WBRT	40/87	**4.1** (2.9, 8.1)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test.

Survival Analysis in the Subgroup of Patients with NSCLC/Breast Primary Enrolled Before Addition of Co-primary

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	31/67	**4.9** (3.0, 9.4)	0.675 (0.396, 1.152)	**0.1460**
RSR13 + WBRT	24/67	**7.6** (4.0, ---)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test.

Appendix 5: Interim Analysis Results

Interim Survival Analysis in All Patients using Cut-off Date of 3/22/2002 (FDA Analysis)

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	122/204	**4.4** (3.6, 5.5)	0.750 (0.576, 0.976)	**0.0314**
RSR13 + WBRT	102/206	**5.7** (4.0, 7.1)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test.

Interim Survival Analysis in the Subgroup of Patients with NSCLC/Breast Primary using Cut-off Date of 3/22/2002 (FDA Analysis)

Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
WBRT	93/157	**4.5** (3.6, 5.6)	0.694 (0.511, 0.942)	**0.0157**
RSR13 + WBRT	75/161	**5.9** (4.3, 8.1)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of RSR13 + WBRT/ WBRT;
[3]: unadjusted log-rank test.

Appendix 6: Exploratory Covariate Adjusted Survival Analyses in NSCLC/Breast Primary

Cox's Proportional Hazard Model Adjusting for Covariates: Protocol Planned Model (N = 414)

Covariates	Hazard Ratio	95% C.I.	P-value[1]
Treatment (RSR13 + WBRT/WBRT)	0.780	0.627, 0.970	0.0253
RPA Class (1 vs. 2)	0.596	0.353, 1.005	0.0522
Primary Tumor Control (Yes vs. No)	1.591	1.138, 2.224	0.0066
Age	1.021	1.011, 1.032	< 0.0001
Presence of Extracranial Metastases (No vs. Yes)	1.403	0.934, 2.107	0.1033
Baseline KPS	0.970	0.959, 0.982	< 0.0001
Number of Metastatic Lesions[2]	1.087	0.916, 1.289	0.3390

1: P-values not adjusted for multiplicity; 2: Since all patients were supposed to have brain metastases, for the purpose of this analysis 'number of extracranial metastases' was used as the covariate in place of 'number of metastatic lesions'.

Table 11: Cox's Proportional Hazard Model Adjusting for Covariates in the Eligible Patient Population: SAP Planned Model*

Covariates	Hazard Ratio	95% C.I.	P-value[1]
Treatment (RSR13 + WBRT/WBRT)	0.781	0.626, 0.974	0.0280
RPA Class (1 vs. 2)	0.601	0.347, 1.042	0.0698
Primary Tumor Control (Yes vs. No)	1.431	0.989, 2.076	0.0573
Age Group (< 65 vs. = 65)	1.748	1.342, 2.277	< 0.0001
Baseline KPS Group (= 90 vs. < 90)	1.543	1.226, 1.941	0.0002
Number of Cranial Metastases	1.130	0.965, 1.323	0.1298
Number of Extracranial Metastases	1.171	1.030, 1.331	0.0156
Baseline Cranial Tumor Total Area (<250, 250-1000, >1000)	1.031	0.883, 1.204	0.8019
Baseline Weight Group (Low vs. High)	0.966	0.738, 1.264	0.7890
Gender (Female vs. Male)	1.504	1.153, 1.961	0.0026
Presence of Liver Metastases (No vs. Yes)	1.237	0.877, 1.745	0.2257
Usage of Subsequent Treatment (No vs. Yes)	0.977	0.714, 1.336	0.8831
Diagnosis Timing (Metachronous vs. Synchronous)	1.169	0.878, 1.555	0.2851
Prior Treatment to Cranial Metastases (No vs. Yes)	0.462	0.275, 0.776	0.0035
Worldwide Location: USA (No vs. Yes) Canada (No vs. Yes)	0.910 0.995	0.623, 1.329 0.653, 1.516	0.6265 0.9816
Altitude (Low vs. High)	1.084	0.743, 1.583	0.6745
Baseline Hemoglobin Group (= 12 vs. < 12 g/dL)	1.296	0.951, 1.765	0.1004
Size of Center (Not a big site vs. Big site)	1.074	0.813, 1.419	0.6141

*: Results based on a total of 408 patients; [1]: P-values not adjusted for multiplicity;

Appendix 7: Exploratory Covariate Adjusted Survival Analysis in Breast Primary

Cox's Proportional Hazard Model Adjusting for Covariates: Protocol Planned Model (N = 115)

Covariates	Hazard Ratio	95% C.I.	P-value[1]
Treatment (RSR13 + WBRT/WBRT)	0.510	0.329, 0.791	0.0027
RPA Class (1 vs. 2)	0.864	0.203, 3.675	0.8433
Primary Tumor Control (Yes vs. No)	1.415	0.802, 2.494	0.2304
Age	1.022	1.001, 1.044	0.0382
Presence of Extracranial Metastases (No vs. Yes)	1.446	0.411, 5.090	0.5660
Baseline KPS	0.966	0.941, 0.992	0.0115
Number of Metastatic Lesions[2]	1.031	0.755, 1.408	0.8461

1: P-values not adjusted for multiplicity; 2: Since all patients were supposed to have brain metastases, for the purpose of this analysis 'number of extracranial metastases' was used as the covariate in place of 'number of metastatic lesions'.

Table 11: Cox's Proportional Hazard Model Adjusting for Covariates in the Eligible Patient Population: SAP Planned Model*

Covariates	Hazard Ratio	95% C.I.	P-value[1]
Treatment (RSR13 + WBRT/WBRT)	0.481	0.289, 0.801	0.0049
RPA Class (1 vs. 2)	0.718	0.209, 2.461	0.5978
Primary Tumor Control (Yes vs. No)	1.381	0.687, 2.778	0.3651
Age Group (< 65 vs. = 65 yrs)	2.970	1.592, 5.542	0.0006
Baseline KPS Group (= 90 vs. < 90)	1.965	1.177, 3.281	0.0098
Number of Cranial Metastases	0.971	0.681, 1.385	0.8706
Number of Extracranial Metastases	1.010	0.753, 1.353	0.9481
Baseline Cranial Tumor Total Area (<250, 250-1000, >1000)	0.939	1.000, 1.000	0.7385
Baseline Weight Group (Low vs. High)	0.852	0.651, 1.356	0.5263
Gender (Female vs. Male)	0.210	0.021, 2.137	0.1874
Presence of Liver Metastases (No vs. Yes)	1.582	0.928, 2.698	0.0919
Usage of Subsequent Treatment (No vs. Yes)	0.669	0.340, 1.316	0.2443
Diagnosis Timing (metachronous vs. synchronous)	0.933	0.264, 3.293	0.9142
Prior Treatment to Cranial Metastases (No vs. Yes)	2.570	0.785, 8.414	0.1189
Worldwide Location: USA (No vs. Yes) Canada (No vs. Yes)	0.597 1.075	0.280, 1.275 0.404, 2.860	0.1827 0.8841
Altitude (Low vs. High)	1.063	0.369, 3.066	0.9095
Baseline Hemoglobin Group (= 12 vs. < 12 g/dL)	1.367	0.748, 2.499	0.3100
Size of Center (Not a big site vs. Big site)	1.346	0.711, 2.546	0.3612

*: Results based on a total of 113 patients; [1]: P-values not adjusted for multiplicity;

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Rajeshwari Sridhara, Ph.D.
Date:

Concurring Reviewer: Kooros Mahjoob, Ph.D.,
Acting Director, Division of Biometrics
Date:

cc:
HFD-150/C. Cottrell
HFD-150/K. Ridenhour
HFD-150/R. Dagher
HFD-710/R. Sridhara
HFD-710/K. Mahjoob
HFD-700/S. Dubey
HFD-700/C. Anello

c:\NDA\allos\21611_statrev_RS.doc